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Atypical brain structures as a function of gray matter volume (GMV) and gray matter density (GMD)  
in young adults relating to autism spectrum traits

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**Abstract:**

Individuals with autistic traits are those who present in the normal population with characteristics of social, communication, personality, and cognitive impairments but do not meet the clinical threshold for autism spectrum disorder (ASD). Most studies have focused on the abnormalities in ASD patients rather than on individuals with autistic traits. In this study, we focused on the behaviors of a large sample (N=401) of Chinese individuals with different levels of autistic traits, measured using the Autism Spectrum Quotient (AQ), and applied voxel-based morphometry (VBM) to determine their association to differences in brain structure. The results mainly showed that the correlation between gray matter volume (GMV) and gray matter density (GMD) of the brain and the AQ was significant in these regions: the frontal gyrus, including the left inferior frontal gyrus (IFG), right middle frontal gyrus (MFG), and left superior frontal gyrus (SFG), which is involved in social processing and social reasoning; the bilateral parahippocampal gyrus (PHG), which is involved in socioemotional behaviors and unconscious relational memory encoding; and the right superior parietal lobule (SPL) and inferior parietal lobule (IPL), which are involved in cognitive control and the ability to show attention to detail. These findings reveal that people with autistic traits in the normal population have atypical development in GMV and GMD, which may affect their social functioning and communication ability.

**Key words:** autistic trait; gray matter volume; gray matter density

## 1. Introduction

Autism spectrum disorder (ASD) consists of neurodevelopmental symptoms characterized by core deficits in social functioning but also extending to other cognitive differences (Assaf et al., 2010). The idea of a spectrum captures both the heterogeneity within ASD itself (e.g. from low intelligence to high-functioning) but also captures the principle of continuity of the symptom profile within the general population itself, in which individuals may exhibit autistic traits to a greater or lesser extent. For instance, the parents of autistic children often report increased levels of autistic traits which are not severe enough to merit a formal diagnosis (Wheelwright, Auyeung, Allison, & Baron-Cohen, 2010). Variation in the level of autistic tendencies is often measured using the AQ, Autism Spectrum Quotient (Baron-Cohen, Wheelwright, Skinner, Martin, & Clubley, 2001). This is a self-report measure that asks about the presence of a range of traits and behaviors commonly seen in autism, including poor social understanding, problems in attention switching, greater attention to detail, poor imagination and poor communication skills. There has been considerable previous research exploring brain-differences between ASD and controls using functional imaging (Ikeda et al., 2018; Pelphrey, Morris, & McCarthy, 2005) and structural imaging techniques (Belmonte et al., 2004; Critchley et al., 2000; Deruelle, Hubert, Santos, & Wicker, 2008; Grelotti, Gauthier, & Schultz, 2002; Rojas et al., 2006). However, the study of brain-based individual differences in autistic traits within the general population has received comparatively less attention. This is an important complementary approach that may also have certain advantages. For instance, the overall level of intellectual functioning (a potential confound) is likely to be more homogenous amongst student-based neurotypical sample than an ASD sample. The present study examines differences in grey matter linked to autistic traits using a Chinese version of the AQ. As well as providing important evidence about the neural basis of autistic traits, it provides an important cross-cultural comparison against the far larger volume of research conducted in the West that will potentially contribute to a wider discussion about how autism should be diagnosed and characterized across different cultures (Pang et al., 2018).

Gray matter density represents the relative concentration of gray matter structures in spatially warped images (i.e., the proportion of gray matter relative to all tissue types within a region) (Mechelli, Price, Friston, & Ashburner, 2005), whereas gray matter volume represents the absolute amount of gray matter (Good et al., 2001; Mechelli et al., 2005). Focusing on both absolute gray matter volume and gray matter density may help our understanding of the mechanism of brain and individual's autistic traits.

Previous studies on GMV in autism spectrum disorders have shown inconsistent results (Draganski et al., 2013; Ecker et al., 2012; Krista L. Hyde, Samson, Evans, & Mottron, 2009; M. C. Lai et al., 2013; McAlonan et al., 2002; Toal et al., 2010). Ecker's ASD study showed a GMV increase bilaterally in the anterior temporal and dorsolateral prefrontal regions and significant decrease in occipital and medial parietal regions compared with controls (Ecker et al., 2012). Another ASD study reported significantly

increases GMV in the frontal brain areas and decrease in pre- and post-central gyri (Krista L. Hyde et al., 2009). Another VBM study revealed increased gray matter volume was observed in the autistic group in the left amygdala, the right inferior temporal gyrus and the left middle temporal gyrus, and decreased in the right paracingulate sulcus, the left occipito-temporal cortex and the left inferior frontal sulcus (Abell et al., 1999). McAlonan use spatial extent statistics method to explore the difference between Asperger's syndrome and the GMV, the results showed GMV deficit in three spatially extensive regions including from basal ganglia extending to the thalamus and ventral striatum; within medial frontal lobe and cingulate; the cerebellum (McAlonan et al., 2002). Adults with ASD also had three large clusters significant reduction in GMV, which centered in the right cerebellum extending into the parahippocampal gyrus and fusiform gyrus, the right inferior temporal gyrus extending from the superior temporal gyrus, and the left parahippocampal gyrus, fusiform gyrus and cerebellum (Toal et al., 2010). Lai's brain structure also showing significant interaction and main effects in ASD in the middle temporal gyrus relative to control (M. C. Lai et al., 2013). Another structural and functional analysis reported reduced GMV in the frontal, temporal, and parietal lobe for high functioning autism compared to healthy control, and no clusters of increased GMV in the patient group were detected (Draganski et al., 2013). Additionally Takeuchi's study about empathizing in young adults showed significantly and negatively correlated with GMV in bilateral mPFCs, bilateral superior frontal gyrus, middle frontal gyrus, left inferior frontal gyrus, right superior parietal lobule, medial frontal gyrus, and anterior cingulate gyrus (Takeuchi et al., 2014). A study relevant to pervasive development disorders showed less regional GMV in the right anterior and posterior insula, the right inferior parietal lobule including the intraparietal sulcus compared with the control group (Kosaka et al., 2010).

Similar results were obtained when measuring GMD. A review of VBM study found GMD decreased in the right paracingulate sulcus, and the left inferior frontal gyrus within adults with high-functioning autism (Brambilla, 2003). Three important psychiatric spectra—schizophrenia spectrum disorder (SCZD), autistic spectrum disorder (ASD) and obsessive-compulsive disorder (OCD), it was found that the GMD of patients did not develop randomly but rather followed identifiable patterns of coalteration (Cauda et al., 2018). A study investigated the change in the developmental trajectories of the striatum in patients with autism and found that developmental trajectories differed between subjects with autism and control subjects in the caudate nucleus, putamen and nucleus accumbens (Langen et al., 2009). Another study on the VBM of patients with high functioning autism showed decreased gray matter density in the ventromedial aspects of the temporal cortex, suggesting an involvement of these areas in the pathophysiology of autism (Kwon, Ow, Pedatella, Lotspeich, & Reiss, 2004). Neural correlates of executive function in autistic spectrum disorders shown significantly increased in the orbital frontal gyrus compared with control groups, moreover in individuals with ASD, increased frontal gray matter density and increased functional activation shared the same anatomical location (Schmitz et al., 2006). Another study explore the relationship between autism and schizophrenia patients

within gray matter and white matter found inverse gray matter density changes in autism relative to healthy controls (Katz et al., 2016). Additionally, regional GMD is correlated with emotional intelligence which showed a significant negative relationship between intrapersonal factor and GMD, including in the medial prefrontal cortex, and also found significant negative correlations between the situation management factor and GMD in the ventromedial prefrontal cortex (Takeuchi et al., 2011). Yamasaki's research also found results that are in line with previously reported structural abnormalities, including reduced gray matter density (Yamasaki et al., 2010).

Autistic spectrum disorder has special characteristics mainly refer to social deficits, communication disabilities, and repetitive and stereotyped behaviors (Hadjikhani, Joseph, Snyder, & Tager-Flusberg, 2005; Troyb et al., 2016). These changes in behavior and mental health are thought to be etiological factors reflected by brain maturation and anatomy (Belmonte et al., 2004; Schmeisser & Boeckers, 2017). While people with autistic traits are not meaningful at a clinical level, they do have an impact on their emotion control, social communication and interaction (Sucksmith, Roth, & Hoekstra, 2011). Individuals with autistic traits undertake the same social responsibilities as normal individuals, but psychologically suffer more pain; they are doing the same job as everyone else but taking up more cognitive resources (Lai, Lombardo, Chakrabarti, & Baron-Cohen, 2013; Sucksmith et al., 2011). Research into autistic tendencies may result, to some extent, in helping this group ease their burdens and obtain a better, healthier life, and therefore preventing a regression to sub-optimal clinical health conditions (Guan & Zhao, 2015). The atypical changes in GMV and GMD, especially in the frontal lobe, lingual gyrus, occipital gyrus, anterior cingulate cortex, insula, and parahippocampus during childhood even adulthood in patients with ASD may reflect that the frontal and lingual regions of the human brain play important roles in planning, self-control, emotional evaluation, and social communication, of which affect an individual's brain and behavioral development. As mentioned above, these studies of VBM have been mostly demonstrated on ASD patients but have rarely focused on individuals varying in their levels of autistic traits, especially in the Chinese sample. Therefore, in this study, participants from underwent structural MRI scans after performing an AQ test. AQ scores were then assessed in relation to GMV and GMD after brain scanning. We hypothesized that the GMV and GMD of the frontal gyrus and parietal gyrus in GMV and GMD would increase as AQ scores increased in individuals with autistic traits since they require more cognitive resources to perform the same work or task as a neurotypical person. This may also be because gray matter maturation is abnormal, while normal gray matter development increases at earlier ages, followed by sustained loss starting around puberty (Gogtay & Thompson, 2010), which may also lead to atypical gray matter development.

## **2. Methods**

### **2.1 Participants**

Four hundred and one individuals (111 men, aged 18-26 years, mean = 21.04 years, standard deviation = 1.27) participated in this research as part of our project investigating associations among genes, brain imaging and mental health (Liu et al., 2017). All participants were right-handed, had normal vision, had no history of psychiatric or neurological illness and were undergraduates at Southwest University. After providing written informed consent, participants received payment for their time. The Brain Imaging Center Institutional Review Board of Southwest China University approved this study and the experimental procedure.

## **2.2 Assessment of AQ**

The AQ is a quantitative measure of autistic traits in the general population (Baron-Cohen et al., 2001). The Chinese version of AQ (Lau et al., 2013) was used in this study which consists of the Social Skill, Communication, Attention Switching, Imagination and Attention to Detail subscales contained within fifty statements, to which participants responded on a 4-point Likert scale, definitely agree or slightly agree responses scored one point, while “slightly disagree” or “definitely disagree” responses scored one point in reverse options. In half of the statements the diagnostic answer is “agree”, and in the other half “disagree”. One point is awarded for each diagnostic answer which results in a continuous distribution of scores in the population sample. The total score ranges from 0 to 50 points, with higher scores suggesting a greater magnitude of autistic traits. Currently available data from research on the properties of this scale indicate that the measurement reliability for the total score is satisfactory (Austin, 2005; Hoekstra, Bartels, Cath, & Boomsma, 2008; Hurst, Mitchell, Kimbrel, Kwapil, & Nelson-Gray, 2007; Ingersoll, Hopwood, Wainer, & Brent Donnellan, 2011; Kloosterman, Keefer, Kelley, Summerfeldt, & Parker, 2011). In the present study we focused on analyzing the total AQ score.

## **2.3 Image acquisition**

A 3-T Siemens Trio MRI scanner (Siemens Medical, Erlangen, Germany) was used to gather images. Then high-resolution T1-weighted structural images (repetition time = 1900 ms, inversion time = 900 ms, flip angle = 9 degrees, echo time = 2.52 ms,  $256 \times 256$  matrix, 176 slices, 1.0 mm slice thickness, and voxel size =  $1 \times 1 \times 1$  mm<sup>3</sup>) were collected, and which a magnetization-prepared rapid gradient echo (MPRAGE) sequence was used.

## **2.4 MRI preprocessing**

The structural MR images were processed with SPM8 ([www.fil.ion.ucl.ac.uk/spm](http://www.fil.ion.ucl.ac.uk/spm)) implemented in MATLAB R2014a (MathWorks Inc., Natick, MA, USA). First, every magnetic resonance image was displayed in SPM8 to monitor artifacts and obvious anatomical abnormalities. Then, VBM was performed with diffeomorphic anatomical registration using exponentiated lie algebra (DARTEL) (Ashburner, 2007). The New

Segment Toolbox from SPM8 was applied to every T1-weighted MR image to extract tissue maps corresponding to gray matter, white matter and cerebrospinal fluid in the native space. The DARTEL template-creation toolbox was used to improve intersubject alignment. The resliced images of the gray and white matter were registered to a subject-specific template and subsequently the normalization function in the DARTEL toolbox was used to normalize the individual images of gray and white matter to the MNI space (1.5-mm isotropic voxels). Finally, each subject's gray and white matter maps were warped using their corresponding smoothed (10-mm full-width at half-maximum (FWHM) Gaussian kernel), reversible deformation parameters to the custom template space and then to the MNI standard space. Gray matter volume (GMV) images were modulated by calculating the Jacobian determinants derived from the special normalization step and by multiplying each voxel by the relative change in volume.

## 2.5 Statistical analysis

We applied multiple linear regression to identify the brain regions whose GMVs and GMDs were associated with individual differences in the AQ within SPM8. In this study a custom binary mask was used to avoid the partial volume effect by including voxels with a gray matter value greater than 0.2. All subsequent statistical analyses were conducted in this mask. To remove potential confounds, we used age, and total GMV and GMD mean values as nuisance covariates (the latter also accounts for gender-based differences in brain size). Clusters with continuous suprathreshold voxels ( $p < 0.001$ ) were initially identified within the custom mask, and within the alphasim correction for multiple comparison (Yan, Wang, Zuo, & Zang, 2016), the p-maps were thresholded to yield an expected p-value of  $<0.05$ .

## 3. Results

### 3.1 Descriptive statistics

The demographic data and behavioral results are shown in **Table1**. The mean AQ score of the current sample was 19.58, and the standard deviation was 5.27.

**Table1** A summary of the demographic information in the present study

### 3.2 Correlations between GMV and AQ score

After entering age, gender, and global volumes of gray matter as covariates into the regression model, a multiple regression analysis revealed that the AQ (total) score had a significant positive association with the GMV in the left inferior frontal gyrus (IFG) and left lingual gyrus (LG) (peak voxel MNI coordinates: -30, 34.5, -6,  $T = 3.43$ ; -13.5, -75, -1.5,  $T = 3.11$ ) and with the GMV in the right middle occipital gyrus (MOG) and right middle frontal gyrus (MFG) (peak voxel MNI coordinates: 30, -88.5, 0;  $T = 3.21$ ; 33, 48, 1.5,  $T = 3.90$ ) see **Figure1 and Table2**. Additionally, the AQ score had a



significant negative association with the GMV in the bilateral parahippocampal gyrus (PHG) (peak voxel MNI coordinates: L -13.5, 3, -27,  $T = -3.79$ ; R 13.5, 3, -27,  $T = -3.34$ ), and right superior parietal lobule (SPL) (peak voxel MNI coordinates: 10.5, -72, 49.5,  $T = -3.16$ ), see *Figure2 and Table2*

*Figure1 The positive correlation between GMV and AQ score,*

*Figure2 The negative correlation between GMV and AQ score*

*Table 2 The brain regions in GMV significantly correlated with AQ*

### 3.3 Correlations between GMD and AQ score

After entering age, gender, and global density of gray matter as covariates into the regression model, a multiple regression analysis revealed that the AQ (total) score had a significant positive association with the GMD in the right inferior parietal lobule (IPL), left cingulate gyrus (CG), left superior frontal gyrus (SFG) and right middle frontal gyrus (MFG) (peak voxel MNI coordinates: -57, -34.5, 48,  $T = 2.81$ ; -4.5, -9, 51,  $T = 2.70$ ; -45, -1.5, 52.5,  $T = 3.33$ ; 25.5, -6, 63,  $T = 3.60$ ), see *Figure3 and Table3*.

*Figure3 Correlations between GMD and AQ score*

*Table3 The brain regions significantly correlated with AQ*

## 4. Discussion

In this study, we investigated associations between the GMV and GMD of brain structures and the AQ of individuals with autistic traits. Our VBM analysis results showed that the AQ (total) score had a significant positive association with GMV in the left IFG and left LG and with GMV in the right MOG, right MFG. Additionally, a significant negative association between AQ (total) score and GMV in the bilateral parahippocampal gyrus (PHG), and right SPL was detected. The AQ (total) score had a significant positive correlation with the GMD in the right IPL, left CG, left SFG, and right MFG. These findings indicated that people with autistic traits may be involved in impaired higher-order cognitive functions impaired such as social functioning, emotional regulation, and working memory. The development of gray matter in early adults was not comparable with that of normal individuals, instead developing in a region-specific manner coinciding with functional maturation. The atypical development in GMV and GMD in the brain structures of individuals with autistic traits may explain the abnormal neuro and social behaviors some degree.

In the present study, we focused on the brain regions that are closely related to autistic traits. First, the AQ (total) score was significantly and positively correlated with GMV and GMD in an extensive region that included the left IFG, SFG, and right MFG. Many brain regions are associated with deficits in social communication and interaction, and activity in response to social pressure occurs in many areas, particularly in the frontal lobe (Fan et al., 2012; Marsh et al., 2014; Morein-Zamir et al., 2016). The frontal lobe regions are related to some brain functions, such as social communication which is localized in the left IFG and right MFG (K. L. Hyde, Samson, Evans, & Mottron,

2010; Patriquin, DeRamus, Libero, Laird, & Kana, 2016; Stevenson et al., 2018); These regions are also known to be involved in planning, flexibility, executive functioning, and working memory in autism spectrum disorder (Craig et al., 2016; Hill, 2004; Jurado & Rosselli, 2007; Zelazo & Müller, 2002). These findings collectively suggest atypical development in the GMV of the brain. Indeed, neuropsychological and neuroimaging studies performed thus far have suggested the association between people with autistic traits and increases in IFG and MFG volumes may be caused by executive dysfunction (Booth, Charlton, Hughes, & Happe, 2003; Corbett, Constantine, Hendren, Rocke, & Ozonoff, 2009; Craig et al., 2016; Vanegas & Davidson, 2015), as people with autistic traits who have normal intelligence, normal life style, and seemingly normal social interactions are burdened with more social pressure, which may be due to their social executive dysfunction (Bayliss & Tipper, 2005; Christ, Kanne, & Reiersen, 2010). The atypical development in the frontal gyrus could reflect a lack of pruning during the normal growth spurt, leading to excessive preservation of unneeded increases. Such an effect would certainly lead to abnormal structure between individuals with autistic traits and brain regions.

Second, the significant decrease in GMV the bilateral parahippocampal gyrus (PHG), was consistent with previous neuroimaging findings in adults and children with autism (Kosaka et al., 2010; Mueller et al., 2013; Page et al., 2009; Yu et al., 2019). Moreover, severely restricted and repetitive behaviors were associated with the PHG (Hau et al., 2019; Monk et al., 2009; Weng et al., 2010). These two brain regions are implicated in unconscious relational memory encoding, autobiographical memory (Duss et al., 2014; Tanweer, Rathbone, & Souchay, 2010), and socioemotional behaviors (Dawson, 1991; Puiu et al., 2018; Yang et al., 2016) that are abnormal in individuals with autistic traits and in patients with clinical ASD, such as understanding the mental states of others, emotion processing, and language (Barrett, Lindquist, & Gendron, 2007; Grecucci, Rubicondo, Siugzdaitė, Surian, & Job, 2016; Lartseva, Dijkstra, & Buitelaar, 2015). As previously reported, individuals with autistic traits could communicate with others in a normal way but are burdened with more social pressure (El Kaliouby, Picard, & Baron-Cohen, 2006). This may be the reason for the decrease in GMV of the PHG reflected in the current study and may explain atypical behaviors such as poor communication and attention switching within individuals with autistic traits.

Third, we also found that individuals with autistic traits had a decrease in GMV in the right SPL, and a significant increase in GMD in the right IPL. The parietal lobules belong to frontoparietal control (FPC) network (Etienne Koechlin, Basso, Pietrini, Panzer, & Grafman, 1999; Kompus, Hugdahl, Ohman, Marklund, & Nyberg, 2009; Mundy, 2018), and deficits to this phenomenon in brain regions may explain the nonsocial difficulties in individuals with autistic traits, such as repetitive, poorly controlled, poor goal-directed action (de Wit, 2018; Takarae, Luna, Minshew, & Sweeney, 2014). The FPC system has been identified as supporting cognitive control

and decision-making processing (Vincent, Kahn, Snyder, Raichle, & Buckner, 2008), and the IPL is important in cognitive control and attention to detail (E. Koechlin & Hyafil, 2007; Kompus et al., 2009; Qiu et al., 2018). Relative to normal individuals the failure of individuals with autistic traits to process information globally might be argued to follow from problems in shifting between local and global processing (Bogousslavsky, Miklossy, Deruaz, Assal, & Regli, 1987; Frith, 2004; Liss, Mailloux, & Erchull, 2008; Van Eylen, Boets, Steyaert, Wagemans, & Noens, 2018), and a failure of cognitive control may be the neural basis of the autistic traits in these individuals (Vartanian et al., 2018). These atypical social cognitive functions relative to SPL and IPL were found within individuals with autistic traits indicating that social cognition's deficit not only strongly influences people's behavior but also results in a unique neuroanatomical structure. Above all these atypical developments in brain structures, such as the frontal gyrus, parahippocampal gyrus and parietal gyrus, may play a role in social and attention abilities associated with brain function.

## **5. Limitation**

This study has several limitations. One is that, the age range of participants was concentrated between 19 and 26 years old, which does not represent the whole population well. Future research is needed to expand the age range of the sample to confirm our findings. Furthermore, we found many brain structures, in addition to the frontal gyrus, parietal gyrus, and parahippocampal gyrus whose GMV and GMD were strongly associated with autistic trait symptoms. The voxel-based morphometry analysis also found the lingual gyrus, cingulate gyrus and occipital gyrus among others. In normal samples and other neurological disease samples these brain areas play a key role but not, however, in autistic trait sample. In future studies, researchers need to apply more analytical methods and more physiological, psychological and neurological factors to explain the internal mechanism of autism traits.

## **6. Conclusions**

In this study, we found that increased or decreased in GMV and GMD of the frontal gyrus, parietal gyrus, parahippocampal gyrus were associated with autism symptoms by AQ scores. Functional abnormalities in these areas were consistent with the symptoms of autistic traits. This may be because GMV or GMD maturation were abnormal, while under normal conditions gray matter development is increased at earlier ages, followed by sustained loss starting around puberty. The different increases or decreases of GMV and GMD of these brain regions is thought to be associated with more social pressure, and more attention to detail rather than to generalities relative to normal people. The AQ test is a continuous variable; all subjects that took the test obtained a score on some point on this axis, which means that, overall, all humans may have autistic traits, someone in a low degree, while others may up to clinical level. In summary, our study aims to develop a normal population with autistic traits to find a

neural foundation that relate to social adaptation and attention regulation and try to clarify the correlation between brain development and mental health.

## **7. Acknowledgements**

### **Author contributions statement**

Yaxu Yu and Zhiting Ren contributed equally to this work.

### **Conflict of interests**

The authors declare no conflicting interest.

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